are directed to a substantially pure mammalian E5-1 protein, support for which is set forth, e.g., on page 7, lines 14-22; page 15, line 29 through page 16, line 19; and page 37, line 11 through page 43, line 15. Dependent claims 73 and 77 are directed to human E5-1 protein, support for which is set forth, e.g., on page 7, lines 14-22; page 15, line 29 through page 16, line 19; and page 37, line 11 through page 43, line 15. Dependent claims 71, 74-76 and 84-85 are directed to naturally occurring mutant E5-1 protein, support for which is set forth, e.g., on page 16, lines 23-29, and page 41, line 9 through page 43, line 15. Claims 80-82 are directed to E5-1 splice variants, support for which is set forth, e.g., on page 40, lines 14-22, and page 41, lines 1-8.

New claims 86 and 87 are directed to human E5-1 protein, support for which is set forth, e.g., on page 7, lines 14-22; page 15, line 29 through page 16, line 19; and page 37, line 11 through page 43, line 15, of the amended specification. Dependent claims 88-91 are directed to naturally occurring mutants of human E5-1 protein, support for which is set forth, e.g., on page 16, lines 23-29, and page 41, line 9 through page 43, line 15. New claim 92 is directed to substantially pure human E5-1 protein encoded by the nucleic acid sequence shown in SEQ ID NO:137, support for which is set forth, e.g., on page 15, line 29 through page 16, line 19, and page 38, lines 26-27. Claims 93 and 94 are directed to naturally occurring mutant E5-1 protein encoded by the nucleic acid sequence shown in SEQ ID NO:137, support for which may be found, e.g., on page 41, line 9 through page 43, line 15, and page 93, lines 3-4 and 19-28. Accordingly, no new matter has been added. Entry of the amendment is respectfully requested.

Previously, the Examiner concluded that Applicants' disclosure of a single species (human) does not enable the genus of mammalian E5-1 proteins. In essence, the Examiner cast doubt on the veracity or accuracy of the statements in the specification relating to the existence of other mammalian E5-1 genes and the relative ease with which they could be isolated.

Applicants respectfully request reconsideration. It is submitted that a person skilled in the art, armed with the teachings of the applicants' disclosure, would have been able to identify and isolate other mammalian E5-1 genes without undue experimentation. Even though a single E5-1 species is disclosed, the present specification establishes the threshold level of predictability that could have allowed a person skilled in the art to isolate other embodiments embraced by the claims by using Applicants' teachings in accordance with standard techniques.

There is no "bright line" test for the number of species that need to be disclosed in order to enable a claim directed to a genus. The law is equally clear that the guidance provided in the specification does not need to be in terms of specific working examples but may be provided by way of "broad terminology". *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). In addition, the law does not require Applicants to disclose each and every embodiment embraced by the claims, even in an unpredictable art. Further, the disclosure must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein. *Id.* It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *Id.* at 370.

The specification teaches human and mouse Alzheimer's Related Membrane Protein (ARMP), now known as PS1 proteins. The specification also teaches that the human E5-1 protein, now known as the PS2 protein, was identified by analyzing a human genome using a probe corresponding to a fragment of the human ARMP. Applicants then discovered that these respective proteins share substantial similarity at both the nucleotide and amino acid levels. *See* the disclosure on page 39, line 3 – page 40, line 22, and in Table 8 of the amended

specification. At pages 45-48, the amended specification contains further teachings with respect to identifying other mammalian homologues.

In further support of their position, Applicants submit herewith a copy of the abstract of *Calenda et al.*, "Cloning of the presenilin 2 cDNA and its distribution in brain of the primate, Microcebus murinus: coexpression with betaAPP and Tau proteins," *Neurobiol. Dis.* 5(5):323-33 (1998). As the Examiner will appreciate, *Calenda* teaches the identification and isolation of a mammalian PS2 gene in accordance with the teachings of the instant specification. Further, the rat and mouse PS2 genes have been sequenced and disclosed in GenBank. See the attachment to the Amendment filed November 11, 1998. In view of the foregoing, reconsideration and withdrawal of the rejection are requested.

Applicants wish to further address the Examiner's earlier position that only the specific mutants disclosed in the specification are enabled. Based upon Applicants' discovery of the E5-1 gene and protein, the identification of two naturally occurring mutant E5-1 proteins and their association with early onset familial Alzheimer's Disease, and the methods disclosed in the specification, any naturally occurring mutant E5-1 protein may be identified without undue experimentation.

Applicants submit that the present amendment and accompanying remarks serve to place the claims in condition for allowance. An early notice to this effect is earnestly solicited. The Examiner is encouraged to contact the undersigned if she has any questions or requests additional information.

Respectfully submitted,

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